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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,223	06/13/2001	Izumu Saito	Q63988	5950

7590 06/03/2004

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EXAMINER	
HILL, MYRON G	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,223	SAITO ET AL.	
	Examiner	Art Unit	
	Myron G. Hill	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45- 78* is/are pending in the application.

4a) Of the above claim(s) *73- 78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45- 72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11 Apr. 01 + 26 Nov 02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/29/03 has been entered.

Election/Restrictions

Newly submitted claims 73- 78 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are drawn to methods of producing Cre in a Flp dependent manner that do not fall within the scope of the previously examined claims.

Since applicant has received an action on the merits for the originally presented invention (Lack of Unity was shown in the Restriction Requirement, dated 8/13/02, and the first product and first method of using were elected), this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 73- 78 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

This action is on claims 45- 72.

Information Disclosure Statement

Enclosed are signed and initialed copies of IDSs indicated by Applicant in the previous response as missing or incomplete (IDS of 11 April 2001 and IDS of 26 November 2002 with WO document initialed).

Rejections Withdrawn

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of claims 1- 12 and 21- 42 under 35 U.S.C. 103(a) as being unpatentable over Hardy (WO 97/32481) and Wahl et al. (WO 92/15694) is withdrawn.

These claims have been cancelled. A new rejection based on the amended claims and addressing Applicant's arguments follows under New Rejections

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45- 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear in claim 45 if the recombinant adenovirus vector (last line) produces the helper virus and it seems that the vector itself is produced, not a "vector expressing a desired protein". In claim 47 it is not clear what "derives" does to the cell or is the cell no longer a 293 cell?

In claims 51, 60, and 65, they are not clear and/or do not further limit the claims from which they depend. It recites the cell comprises a poly A sequence or a nucleotide sequence and a poly A sequence. It would be more clear if the claims were to recite something to the effect of the cell of claim X wherein the stuffer sequence comprises etc. Is the desired protein of claim 45 the same as those recited in claims 51, 60, and 65?

Claim 45 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: elements that define the Cre function. The claim indicates that Cre is regulated but does not provide any structure for the recited function.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45- 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy (WO 97/32481, from IDS), and Akagi *et al.* (NAR 1997 Vol. 25, No. 9, pages 1766- 1773), in view of Wahl *et al.* (WO 92/15694, from IDS).

In the rejection of the previous claims Applicant agued the following: the claimed invention is extremely useful in a helper dependent adenovirus vector system and listed structural elements that are disclosed in the specification and details the functional usefulness of Cre as disclosed in the specification for making adenovirus vectors, and comments on the teaching of Hardy. Applicant agues that Hardy is concerned with Cre as it acts on the helper virus and not on the Cre expressing cell *per se*. Applicant also argues that Hardy solves a different problem and that famous researchers in the art have also used the same conventional Cre expressing cells. And finally, that there is no motivation to combine Wahl *et al.* with Hardy to solve the problem.

Applicant's arguments have been fully considered and not found persuasive.

Many of the limitations referred to by Applicant are not in the claims or not in a combination of the claims. Other elements are discussed below. The claims have been amended and presented as new in the current set of claims and a new rejection is set forth below.

The invention is drawn to a cell that expresses Cre in a Flp dependent manner wherein the Flp is supplied by an adenovirus vector and the cell is used to produce helper dependent adenovirus vectors.

Hardy teaches a cell that expresses Cre and that is used to make helper dependent adenovirus vectors (abstract and whole document). Hardy teaches Cre expressing host cells and these can be made by any number of ways known in the art (page 23, lines 11 and 12). Hardy teaches a nuclear localization signal for transport to the nucleus of message (page 23, lines 22 and 23). Hardy also teaches that there is the

possibility that if Cre is expressed all the time, there could be a negative selective pressure towards what the Cre is acting on, that functionally expressed Cre is needed, and that functional Cre expressing cells can be made by many ways that are well known in the art (page 14, lines 6- 31, page 23, lines 11- 23, and Example 3 starting on page 31) and that cells. Hardy discloses that it is not advantageous to grow recombinant virus in a cell expressing Cre all the time (in particular page 14, lines 26- 31). Hardy uses a 293 cell line that does not produce Cre in parts 1 and 2 of the method to produce recombinant adenovirus and use a 293 cell line that expresses Cre in the part 3 of the method.

Hardy does not teach recombinase Flp as a way to regulate expression of Cre.

Akagi *et al.* teach that adenovirus vectors expressing a recombinase can be used to control the expression of specific genes that are integrated into the chromosomes of cells and that both Cre and Flp are known recombinases (abstract). Akagi *et al.* teach the use of hybrid CAG promoter (comprising CMV enhancer, chicken beta actin promoter and a rabbit beta actin promoter) and rabbit poly A signal (page 1782, column 1, middle and Figure 1).

Wahl *et al.* teach recombinase Flp in a site specific gene activation system (specific protein expression) using flp recombinase to control expression of a gene product in a manner that depends on expression of recombinase flp. This expression system uses a stuffer DNA (neomycin) which is flanked by frt sites and which suppresses the expression of the downstream gene, and excision of the neomycin by recombinase flp leads to expression of the downstream gene. When the cell containing

this expression cassette has recombinase flp introduced into it, the nucleic acid sequences upstream of the gene of interest are removed by the specific action of the recombinase and the gene of interest is now expressed (page 4, lines 20- 28, page 22 line 18- page 23, line 25, and Figure 1B).

One of ordinary skill in the art would know that there are many enhancers, promoters, splice acceptor, and a poly A signals that function in 293 cells are known in the art and selection of the specific ones would be a matter of routine optimization. One of ordinary skill in the art at the time of invention would have known that Cre expressing cells could also be made by stable integration into the genome of gene to be expressed as taught in Akagi *et al.* Hardy is not limited to only using adenovirus to deliver Cre. One of ordinary skill in the art at the time of invention would have known that Cre could be regulated and that the adenovirus of Akagi *et al.* could be modified to use the other recombinase, Flp, to regulate Cre because Cre could not be used to regulate itself. Akagi *et al.* creates transgenic cells in an animal; however, the same could be used for a stable cell line and the use of neomycin as a selectable marker for episomes or chromosomal integration is well known and a routine practice in the lab. Knowing that recombinase Flp is needed to be expressed in the cells to obtain Cre expression, one of ordinary skill in the art would know that expression of an exogenous protein can be achieved by infection with a recombinant adenoviral expression vector that expresses recombinase Flp. One of skill in the art at the time of invention would have been motivated to regulate Cre expression because it would save steps from the method taught by Hardy.

The reason for the problem solved in the instant invention is not different from the prior art because the problem of Hardy is a problem of Cre in the cell *per se* not just with the *lox* site as argued by applicant.

Thus, it would be *prima facie* obvious to control the expression of Cre in a Cre expressing cell as taught by Hardy with the adenovirus of Akagi *et al.* with the expectation of success in making a cell that produces Cre in a Flp dependent manner.

Conclusion

No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Myron G. Hill whose telephone number is 571-272-0901. The examiner can normally be reached on 9am-6pm Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Myron G. Hill
Patent Examiner
June 1, 2004

JEFFREY STUCKER
PRIMARY EXAMINER